



## FEP Medical Policy Manual

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### FEP 2.04.143 Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

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**Original Policy Date: April 2018**

#### **Related Policies:**

2.04.125 - Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer  
2.04.141 - Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)  
2.04.45 - Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

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## Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)

### Description

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Genetic testing of circulating tumor DNA and circulating tumor cells in peripheral blood (referred to as "liquid biopsy") potentially offers a noninvasive alternative to tissue biopsy for therapeutic decisions and prognosis in patients with cancer. For patients with non-small-cell lung cancer, the detection of "driver mutations" or resistance variants is important for selecting patients for targeted therapy.

#### Predictive Biomarkers in Non-Small-Cell Lung Cancer

Several predictive genetic biomarkers have been identified for NSCLC. Somatic genome alterations known as "driver mutations" are usually transformative variants arising in cancer cells in genes encoding for proteins important in cell growth and survival. Randomized controlled trials have demonstrated improved efficacy, often in conjunction with decreased toxicity, of matching targeted therapies to patients with specific driver mutations. Several such targeted therapies are approved by the U.S. Food and Drug Administration (FDA) for NSCLC. Guidelines generally suggest the analysis of either the primary NSCLC tumor or of metastasis for the presence of a set of driver mutations to select an appropriate treatment.

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## Genetic Biomarkers With FDA Approved Targeted Therapies

The list of targeted therapies approved for NSCLC is evolving. Currently, there are FDA approved targeted therapies for epidermal growth factor receptor (*EGFR*) variants, anaplastic lymphoma kinase (*ALK*) translocations, *ROS1* translocations, and *BRAF* variants for NSCLC. Companion diagnostics using tissue samples have also been FDA approved to identify the associated driver mutations for the targeted therapies. The evaluation of molecular analysis of tissue samples for targeted therapy of NSCLC is found in evidence review 2.04.45.

### *EGFR* Variants

Specific *EGFR* variants confer sensitivity to treatment with tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib; the most common variants are deletions in exons 19 and an exon 21 substitution variant (L858R). These variants are referred to as TKI-sensitizing variants and are found in approximately 10% of white patients and up to 50% of Asian patients. The prevalence of *EGFR* variants is not well characterized in other ethnic or racial groups but is estimated to be 10% to 15% in studies including general U.S. populations. TKIs are indicated as first-line treatment for patients with sensitizing variants; progression-free survival is improved with the use of TKIs. Patients receiving TKIs have fewer treatment-related adverse events than patients receiving cytotoxic chemotherapy.

### *ALK* and *ROS1* Translocations

*ALK* rearrangements confer resistance to TKIs. Approximately 4% of patients have *ALK* rearrangements. The TKI crizotinib, an inhibitor of *ALK*, *ROS1*, and mesenchymal-epithelial transition (*MET*) tyrosine kinases, is indicated in patients with *ALK*-positive tumors. In randomized trials comparing crizotinib with standard chemotherapy in *ALK*-positive patients, crizotinib has been associated with improved progression-free survival, response rates, lung cancer symptoms, and quality of life. *ROS1* rearrangements develop in 1% to 2% of patients. For such patients, crizotinib has been shown to be effective, with response rates of about 70%.

### *BRAF* Variants

*RAF* proteins are serine/threonine kinases that are downstream of *RAS* in the *RAS*-*RAF*-*ERK*-*MAPK* pathway. In this pathway, the *BRAF* gene is the most frequently mutated in NSCLC, in 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. *BRAF* or *MEK* inhibition with TKIs (eg, vemurafenib/dabrafenib or trametinib) was originally approved by the FDA for treatment of unresectable or metastatic melanoma with *BRAF* V600 variants but the combination of dabrafenib and trametinib was expanded to include treatment of metastatic NSCLC in 2017.

### *MET* Variants

C-*MET*, the hepatocyte growth factor (HGF) receptor, is a tyrosine kinase receptor that is involved in cell survival and proliferation. *MET* (mesenchymal-epithelial transition) amplification is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to *EGFR* TKIs. *MET* amplification occurs in 2% to 4% of treatment-naïve NSCLC and *MET* and *EGFR* commutations occur in 5% to 20% of NSCLC tumors with acquired resistance to *EGFR* TKIs. *MET* exon 14 (*MET*ex14) skipping mutations occur in approximately 3-4% of adenocarcinomas and 1-2% of patients with other NSCLC histologies. Higher frequencies are observed in older women who are nonsmokers. *MET*ex14 genomic alterations do not typically overlap with *EGFR*, *ROS1*, *BRAF*, and *ALK* variants. Several types of *MET*ex14 skipping mutations can occur, including mutations, base substitutions, and deletions. *MET* inhibition with capmatinib was granted accelerated approval by the FDA in 2020 for treatment of metastatic NSCLC in patients positive for *MET*ex14 skipping mutations based on results from an open-label, non-randomized, phase 2 trial in 97 subjects (NCT02414139). Among 28 treatment-naïve patients, the overall response rate (ORR) was 68% with a response duration of 12.6 months. Among 69 previously treated patients, the ORR was 41% with a response duration of 9.7 months. Patients in this study were wild-type for *EGFR* variants and negative for *ALK* rearrangements.

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## RET Fusions

*RET* (rearranged during transfection) is a proto-oncogene that encodes a receptor tyrosine kinase growth factor. *RET* fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas. *RET* inhibition with pralsetinib was granted accelerated approval by the FDA in 2020 for treatment of metastatic *RET*-fusion-positive NSCLC. Approval was based on results from an open-label, non-randomized phase 1/2 trial in 114 patients (NCT03037385). Among 27 treatment-naïve patients, the ORR was 70% with 58% of responses lasting 6 months or longer in duration. Among 87 patients previously treated with chemotherapy, the ORR was 57% with 80% of responses lasting 6 months or longer in duration. *RET* inhibition with selpercatinib was granted accelerated approval by the FDA in 2020 for the treatment of *RET* fusion-positive metastatic NSCLC and advanced or metastatic medullary thyroid cancer. Approval for NSCLC was based on results from an open-label, non-randomized phase 1/2 trial in 144 patients (NCT03157128). Among 39 treatment-naïve patients, the ORR was 85% with 58% of responses lasting 6 months or longer in duration. Among 105 patients previously treated with platinum chemotherapy, the ORR was 64% with 81% of responses lasting 6 months or longer in duration.

## Genetic Biomarkers With Off-Label Targeted Therapies

Proposed targeted therapies may be used off-label for genetic alterations in human epidermal growth factor receptor 2 (trastuzumab, afatinib), *MET* (crizotinib), and *RET* (cabozantinib, vandetanib). Human epidermal growth factor receptor 2 is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. Human epidermal growth factor receptor 2 is expressed in approximately 25% of NSCLC.

## Genetic Biomarkers Without Targeted Therapies

The most common predictive variant in North American populations is *KRAS*, occurring in 20% to 25% of NSCLC. Patients with *KRAS* variants have shorter survival than those without *KRAS* variants, and thus *KRAS* is a prognostic marker. It also predicts a lack of TKI efficacy. Because *KRAS* variants are generally not found with other tumor biomarkers, *KRAS* testing might identify patients who would not benefit from further molecular testing. Targeted therapies are under investigation for *KRAS*-variant NSCLC.

## Tyrosine Kinase Inhibitor-Resistance Variants

### EGFR Variants

The *EGFR* variant T790M has been associated with acquired resistance to TKI therapy. When the T790M variant is detected in tissue biopsies from patients with suspected resistance to TKI therapy, osimertinib is recommended as second-line therapy. The use of osimertinib as first-line therapy for patients who have *EGFR*-sensitizing variants was approved by the FDA in 2018 on the basis of the randomized, double-blind phase 3 FLAURA trial (see Table 6).

## Treatment Selection

### Tissue Biopsy as a Reference Standard

The standard for treatment selection in NSCLC is biomarker analysis of tissue samples obtained by biopsy or surgery. However, a lung biopsy is invasive with a slow turnaround time for obtaining results. Tissue biopsy may also be an imperfect reference standard due to inadequate sampling, tumor heterogeneity, or other factors.

## Technologies for Detecting Circulating Tumor DNA

Cell-free DNA in blood is derived from nonmalignant and malignant cell DNA. The small DNA fragments released into the blood by tumor cells are referred to as circulating tumor DNA (ctDNA). Most ctDNA is derived from apoptotic and necrotic cells, either from the

primary tumor, metastases or circulating tumor cells.<sup>1</sup> Unlike apoptosis, necrosis is considered a pathologic process, generating larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origins. The ctDNA can be used for genomic characterization of the tumor and identification of the biomarkers of interest.

Detection of ctDNA is challenging because cell-free DNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cell-free DNA. Therefore, methods up to 500 to 1000 times more sensitive than standard sequencing approaches (eg, Sanger) are needed.

Sensitive and specific methods are available to detect ctDNA and identify single nucleotide variants, duplications, insertions, deletions, and structural variants. Examples of methods are as follows:

- Denaturing high-performance liquid chromatography involves polymerase chain reaction (PCR) followed by denaturing plus hybridization and then separation.
- Peptide nucleic acid-locked nucleic acid PCR suppresses wild-type *EGFR* followed by enrichment for mutated *EGFR*.
- Amplification refractory mutation system PCR generates different-sized PCR products based on the allele followed by separation of PCR fragments to determine the presence of variants.
- BEAMing combines emulsion PCR with magnetic beads and flow cytometry.
- Digital genomic technologies, such as droplet digital PCR, allow for the enumeration of rare variants in complex mixtures of DNA.

Genetic testing of ctDNA can be targeted at specific genes or at commonly found, acquired, somatic variants ("hotspots") that occur in specific cancers, which can impact therapy decisions (eg, *EGFR* and *ALK* in NSCLC); such testing can also be untargeted and may include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing. Panel testing for specific genetic variants that may impact therapy decisions in many different cancers can also be performed.

## OBJECTIVE

The objective of this evidence review is to determine whether testing for driver or resistance variants using circulating tumor DNA or other "liquid biopsies" in peripheral blood improves the net health outcome in individuals with non-small-cell lung cancer.

## POLICY STATEMENT

### EGFR TESTING

At diagnosis, only analysis of somatic variants in exons 19 through 21 (eg, exon 19 deletions, L858R, T790M ) within the epidermal growth factor receptor (EGFR) gene, using the cobas EGFR Mutation Test v2, Guardant360 CDx test, OncoBEAM test or InVisionFirst-Lung test with plasma specimens to detect circulating tumor DNA (ctDNA), may be considered **medically necessary** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to an *EGFR* tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], dacomitinib [Vizimpro], or osimertinib [Tagrisso]) in patients with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified.

At progression, analysis of the *EGFR* T790M resistance variant for targeted therapy with osimertinib using ctDNA using the cobas EGFR Mutation Test v2, Guardant360 CDx test, OncoBEAM test or InVisionFirst-Lung test with plasma specimens to detect circulating tumor DNA (ctDNA), may be considered **medically necessary** in patients with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified when tissue biopsy to

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obtain new tissue is not feasible, e.g., in those who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue, do not have a biopsy-amenable lesion, or cannot undergo biopsy. (see Policy Guidelines).

Analysis of other *EGFR* variants within exons 22 to 24, or other applications related to NSCLC, is considered **investigational**.

## Other Genes

Plasma tests for oncogenic driver variants deemed medically necessary on tissue biopsy (see evidence review 2.04.45) may be considered **medically necessary** to predict treatment response to targeted therapy for patients meeting the following criteria:

- Patient does not have sufficient tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; AND
- Follow-up tissue-based analysis is planned should no driver variant be identified via plasma testing.

## ALK TESTING

Analysis of somatic rearrangement variants of the *ALK* gene using plasma specimens to detect ctDNA or RNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori], ceritinib [Zykadia], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with NSCLC.

## BRAF V600E TESTING

Analysis of the *BRAF* V600E variant using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar], trametinib [Mekinist]) in patients with NSCLC.

## ROS1 TESTING

Analysis of somatic rearrangement variants of the *ROS1* gene using plasma specimens to detect ctDNA or RNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with NSCLC.

## MET TESTING

Analysis of the *MET* exon 14 skipping variant using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to MET inhibitor therapy (capmatinib [Tabrecta]) in patients with NSCLC.

## RET TESTING

Analysis of somatic fusion variants of the *RET* gene using plasma specimens to detect ctDNA is considered **investigational** as an alternative to tissue biopsy (see Policy Guidelines) to predict treatment response to RET inhibitor therapy (eg, selpercatinib [Retevmo], pralsetinib [Gavreto]) in patients with NSCLC.

## KRAS TESTING

Analysis of somatic variants of the *KRAS* gene using plasma specimens to detect ctDNA is considered **investigational** as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC.

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## HER2 TESTING

Analysis of alterations in the *HER2* gene using plasma specimens to detect ctDNA for targeted therapy in patients with NSCLC is considered **investigational**.

## POLICY GUIDELINES

The tests discussed herein, cobas EGFR Mutation Test v2, Guardant360 CDx test, Oncobeam test or InVisionFirst-Lung, are intended for use in patients with advanced (stage III or IV) non-small-cell lung cancer. These tests include variants beyond exons 19 through 21 of the epidermal growth factor receptor (*EGFR*) gene, and some tests additionally include variants in numerous other genes. Patients with sensitizing variants of the tyrosine kinase domain of the *EGFR* gene are considered good candidates for treatment with erlotinib, gefitinib, afatinib, dacomitinib, or osimertinib. The U.S. Food and Drug Administration approval for the cobas EGFR Mutation Test v2 states that patients who are negative for *EGFR* exon 19 deletions or L858R variant based on the plasma test should be reflexed to routine biopsy and testing using formalin-fixed paraffin-embedded tissue. Plasma tests for other oncogenic driver variants deemed medically necessary on tissue biopsy (see evidence review 2.04.45) may also be appropriate for patients who do not have enough tissue for standard molecular testing using formalin-fixed paraffin-embedded tissue; however this is only appropriate if follow-up tissue-based analysis is planned should no driver variant be identified.

## Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease

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Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

## BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

## FDA REGULATORY STATUS

In June 2016, cobas EGFR Mutation Test v2 (Roche Molecular Systems), a real-time PCR test, was approved by the FDA through the premarket approval process (P150047).<sup>2</sup> This plasma test is a real-time PCR test approved as a companion diagnostic aid for selecting NSCLC patients who have *EGFR* exon 19 deletions, and L858R substitution variants, for treatment with erlotinib. A premarket approval supplement expanded the indication to include the test as a companion diagnostic for treatment with gefitinib and osimertinib in 2018 (P120019/S019). Patients who test negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for *EGFR* variants.

In August 2020, Guardant360 CDx (Guardant Health), a qualitative next generation sequencing-based diagnostic of circulating cell-free DNA in plasma, was approved by the FDA through the premarket approval process (P200010).<sup>3</sup> The plasma test is approved as a companion diagnostic for selecting NSCLC patients who have *EGFR* exon 19 deletions, L858R substitution variants, or T790M variants, for treatment with osimertinib. Patients who test negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for *EGFR* variants. Testing for T790M using plasma specimens is most appropriate for consideration in patients for whom a tumor biopsy cannot be obtained, as the efficacy of osimertinib has not been established in T790M plasma-positive, tissue-negative or unknown patient populations.

In August 2020, FoundationOne Liquid CDx (Foundation Medicine), a qualitative next generation sequencing-based diagnostic for circulating cell-free DNA in plasma, was approved by the FDA through the premarket approval process (P190032).<sup>4</sup> The plasma test is approved as a companion diagnostic for selecting NSCLC patients who have *EGFR* exon 19 deletions and *EGFR* exon 21 L858R substitution variants, for treatment with gefitinib, osimertinib, or erlotinib. Patients who test negative for the variants detected should be referred for (or "reflexed" to) routine biopsy with tissue testing for *EGFR* variants. Prior versions of FoundationOne Liquid CDx were previously marketed as FoundationACT and FoundationOne laboratory developed test (LDT).

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Several companies market tests that detect tumor markers from peripheral blood, including TKI-sensitizing variants for NSCLC. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test. Clinical laboratories accredited through the College of American Pathologists enroll in proficiency testing programs to measure the accuracy of the test results. There are currently no College of American Pathologists proficiency testing programs available for ctDNA testing to ensure the accuracy of ctDNA laboratory-developed tests.

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## RATIONALE

### Summary of Evidence

For individuals with advanced non-small-cell lung cancer (NSCLC) who receive testing for biomarkers of *EGFR* tyrosine kinase inhibitor (TKIs) sensitivity using circulating tumor DNA (ctDNA) with the cobas *EGFR* Mutation Test v2 (liquid biopsy), the evidence includes numerous studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), and test validity. Current evidence does not permit determining whether cobas or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of cobas. The cobas *EGFR* Mutation Test has adequate evidence of clinical validity for the *EGFR* TKI-sensitizing variants. The U.S. Food and Drug Administration has suggested that a strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the cobas test would result in an overall diagnostic performance equivalent to tissue biopsy. Several additional studies of the clinical validity of cobas have shown it to be moderately sensitive and highly specific compared with a reference standard of tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the cobas test should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with *EGFR* TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. The cobas test can identify patients for whom there is a net benefit of targeted therapy vs chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with advanced NSCLC who receive testing for biomarkers of *EGFR* TKI sensitivity using ctDNA (liquid biopsy) with the Guardant360 CDx, OncoBEAM or InVision tests, the evidence includes several studies assessing the diagnostic characteristics of liquid biopsy compared with tissue. Relevant outcomes are OS, DSS, and test validity. Current evidence does not permit determining whether liquid or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA identified no RCTs providing evidence of the clinical utility of these tests. The Guardant360 CDx, OncoBEAM, and InVision tests have adequate evidence of clinical validity for the *EGFR* TKI-sensitizing variants. A strategy of liquid biopsy followed by referral (reflex) tissue biopsy of negative liquid biopsies for the tests would result in an overall diagnostic performance similar to tissue biopsy. A chain of evidence demonstrates that the reflex testing strategy with the Guardant360 CDx, OncoBEAM or InVision tests should produce outcomes similar to tissue testing while avoiding tissue testing in approximately two-thirds of patients with *EGFR* TKI-sensitizing variants. Patients who cannot undergo tissue biopsy would likely otherwise receive chemotherapy. These tests can identify patients for whom there is a net benefit of targeted therapy vs chemotherapy with high specificity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with advanced NSCLC who receive testing for biomarkers of *EGFR* TKI sensitivity using ctDNA with tests other than the cobas *EGFR* Mutation Test v2, Guardant360 CDx, OncoBEAM or InVision tests, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with tissue reference standard. Relevant outcomes are OS, DSS, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests other than the cobas, Guardant360 CDx, OncoBEAM and InVision tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision. Current evidence does not permit determining whether a liquid biopsy or tissue biopsy is more strongly associated with patient outcomes or treatment response. BCBSA found no RCTs providing evidence of the clinical utility of those methods of liquid biopsy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with advanced NSCLC who receive testing for biomarkers other than *EGFR* using a liquid biopsy to select a targeted therapy, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy compared with the tissue biopsy reference standard. Relevant outcomes are OS, DSS, and test validity. Given the breadth of molecular diagnostic methodologies available to assess ctDNA, the clinical validity of each commercially available test must be established independently. None of the commercially available tests have multiple studies of adequate quality to estimate the performance characteristics with sufficient precision for variants other than *EGFR*. We found no RCTs providing evidence of the clinical utility of those methods of liquid biopsy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with advanced NSCLC who progressed on *EGFR* TKIs who receive testing for biomarkers of *EGFR* TKI resistance using liquid biopsy, the evidence includes studies assessing the diagnostic characteristics of liquid biopsy. Relevant outcomes are OS, DSS, and test validity. For variants that indicate *EGFR* TKI resistance and suitability for alternative treatments with osimertinib, liquid biopsy is moderately sensitive and moderately specific compared with a reference standard of tissue biopsy. Given the moderate clinical sensitivity and specificity of liquid biopsy, using liquid biopsy alone or in combination with tissue biopsy might result in the selection of



different patients testing positive for *EGFR* TKI resistance. It cannot be determined whether patient outcomes are improved. However, although there is higher discordance in the liquid vs tissue results for the resistance variant, retrospective analyses have suggested that patients positive for T790M in liquid biopsy have outcomes with osimertinib that appear to be similar overall to patients positive by a tissue-based assay. The evidence is insufficient to determine the effects of the technology on health outcomes. Although the evidence is limited, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published joint guidelines endorsed by American Society of Clinical Oncology with an expert consensus opinion that physicians may use liquid biopsy (cell-free DNA) to identify *EGFR* T790M variants in patients with progression or resistance to *EGFR*-targeted TKIs and that testing of the tumor sample is recommended if the liquid biopsy result is negative. Similarly, the National Comprehensive Cancer Network guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when testing for the T790M resistance variant, liquid biopsy should be considered and when a liquid biopsy is negative tissue-based testing is strongly recommended.

## SUPPLEMENTAL INFORMATION

### Practice Guidelines and Position Statements

#### National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines (v.8.2020) discuss the role of liquid biopsy in the management of non-small-cell lung cancer (NSCLC).<sup>5</sup> The guidelines state that cell-free/circulating tumor DNA testing should not be used in lieu of histologic tissue diagnosis. They also state that cfDNA testing can be used if the patient is not medically fit for tissue sampling or there is insufficient tissue for molecular analysis. If plasma-based analysis is used, follow-up with tissue-based analysis should be planned if plasma-based analysis is negative. The guidelines also state that at progression on erlotinib, afatinib, gefitinib or dacomitinib when testing for T790M, plasma-based testing should be considered and when plasma-based testing is negative, tissue-based testing is strongly recommended. Scheduling the biopsy concurrently with plasma testing referral may be considered.

The guidelines additionally state that if there is insufficient tissue to allow testing for *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, and *RET*, repeat biopsy and/or plasma testing should be done. If not feasible, treatment should be guided by available results, and if mutation status is unknown, patients are treated as though they do not have driver oncogenes. Diagnosis of NSCLC should be guided by tissue. The guidelines do not endorse any specific commercially available test.

#### International Association for the Study of Lung Cancer

In 2018, the International Association for the Study of Lung Cancer published a statement paper on liquid biopsy for advanced non-small-cell lung cancer.<sup>39</sup> The work preparing the statement was supported by unrestricted grants from Guardant Health, Astra Zeneca, Biocept, and Roche. The statement made the following recommendations:

- "The criteria used to select treatment-naïve patients for molecular testing of ctDNA [circulating tumor DNA] is the same used for molecular testing using DNA isolated from tissue."
- "Liquid biopsy can be considered at the time of initial diagnosis in all patients who need tumor molecular profiling, but it is particularly recommended when tumor tissue is scarce, unavailable, or a significant delay potentially greater than 2 weeks is expected in obtaining tumor tissue."

The following tests are acceptable to detect epidermal growth factor receptor (*EGFR*)-sensitizing variants and results are sufficient to start a first-line treatment with an *EGFR* tyrosine kinase inhibitor:

- Cobas *EGFR* MutationTest v2.
- droplet digital polymerase chain reaction next-generation sequencing panels

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- Multiplex panels using next-generation sequencing platforms could be considered to detect *EGFR*, *ALK*, *ROS1*, or *BRAF* variants and a positive result would be adequate to initiate first-line therapy.

A next-generation sequencing multiplex panel was preferred to detect T790M and other common resistance alterations. A positive result for *EGFR* T790M should be considered adequate to initiate osimertinib in the second-line setting.

## College of American Pathologists et al

In 2018, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published a guideline on molecular testing for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors.<sup>38</sup> The American Society of Clinical Oncology also endorsed the joint College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guidelines with minor modifications.<sup>40</sup>

The guidelines noted the following recommendation regarding liquid biopsy for activating *EGFR* mutations and a consensus opinion regarding liquid biopsy for the T790M resistance mutation.

- Recommendation: "In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify [activating] *EGFR* mutations."
- Expert Consensus Opinion: "Physicians may use plasma cfDNA methods to identify *EGFR* T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to *EGFR* targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative."
- No recommendation: "There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of *EGFR* or other mutations, or the identification of *EGFR* T790M mutations at the time of *EGFR* TKI resistance."

## National Institute for Health and Care Excellence

In 2018, the National Institute for Health and Care Excellence issued an innovation briefing on plasma *EGFR* mutation tests for adults with locally advanced or metastatic NSCLC.<sup>41</sup> The briefing reviewed 7 ctDNA tests available in Europe and concluded:

- "The intended place in therapy would be as an alternative to tissue *EGFR* testing or before tumour testing to inform decisions about prescribing *EGFR*-TKIs. Plasma testing may be particularly useful for people whose disease has developed resistance to an *EGFR*-TKI and who could be offered second-line *EGFR*-TKIs, if appropriate, without having further tissue testing."
- "The main points from the evidence summarised in this briefing are from 7 non-UK-based prospective studies with 2,106 adults. They show that the diagnostic accuracy of plasma *EGFR* mutation testing has a similar specificity, but lower sensitivity, compared with tissue *EGFR* mutation testing in adults with locally advanced or metastatic NSCLC."
- "Key uncertainties around the evidence or technology are that tests for identifying *EGFR*-TKI mutations are rapidly evolving and there is no established gold-standard test against which to evaluate them."

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

Date	Action	Description
March 2018	New policy	Policy created with a literature review through September 11, 2017 based on review presented to BCBSA Medical Advisory Panel in September 2017 (See Appendix 1). Policy statement that the use of cobas circulating tumor DNA for detection of EGFR variants for selection of treatment with EGFR TKI is medically necessary; all other circulating tumor DNA tests are considered not medically necessary; all other NSCLC indications considered not medically necessary.
December 2018	Replace policy	Policy updated with literature review through Aug 8, 2018. References 4-6, 8, 10, 14, 16, 17, 19, and 26 added; reference 25 was updated. Policy statements regarding testing for ALK, ROS1, BRAF, and other variants were added as investigational. Policy statement regarding medically necessary of testing for EGFR-sensitizing variants was expanded to include Guardant360 and OncoBEAM as well as cobas EGFR Mutation Test v2 (Roche Molecular Systems). All other circulating tumor DNA tests and NSCLC indication policy statements revised from not medically necessary to investigational as a correction to align with FDA regulatory status.
December 2019	Replace policy	Policy updated with literature review through August 1, 2019; references added. A medically necessary (MN) statement was added for the commercial test for testing for the EGFR variants. Edits made to the EGFR MN statement to be consistent with the MN statement in the closely related policy on tissue-based EGFR testing in NSCLC (2.04.45).

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Date	Action	Description
March 2021	Revised policy	Policy updated with literature review through July 20, 2020; references added. Individual policy statements regarding testing for MET and RET were added to reflect new targeted therapy approvals and maintained as investigational. Exon 18 was removed from medically necessary EGFR variants to coincide with tissue-based EGFR testing policy in NSCLC (2.04.45) and reflect actionable variants. EGFR policy statement was updated to reflect Guardant360 CDx test version. A medically necessary policy statement was added for patients with insufficient tissue who are being tested for variants deemed medically necessary in 2.04.45.

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